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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/048,196	01/23/2002	Joelle Thonnard	BM45402	2957

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DECHERT
ATTN: ALLEN BLOOM, ESQ
4000 BELL ATLANTIC TOWER
1717 ARCH STREET
PHILADELPHIA, PA 19103

EXAMINER

BASKAR, PADMAVATHI

ART UNIT

PAPER NUMBER

1645

DATE MAILED: 07/15/2003

8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/048,196	THONNARD, JOELLE	
	Examiner Padmavathi v Baskar	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM
 THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 4/22/03.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 27-49 is/are pending in the application.
- 4a) Of the above claim(s) 28,30,31,33,36,37,39-42,45 and 47-48 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 27,29,32,34,35,38,43,44 and 46 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) 27-49 are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
 If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ .
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .	6) <input type="checkbox"/> Other: _____ .

DETAILED ACTION

1. Applicant's response to restriction requirement in Paper No. 7 (4/22/03) is acknowledged. Claims 27-49 are pending in the application.

Priority

2. This application is a 371 OF PCT/EP 00/07291, 7/27/2000 which claims priority under 35, U.S.C. 119 (a)- (d) to U.K 991804.1; 7/30/1999 is acknowledged. Examiner has reviewed all the priority documents and found that the SEQ.ID.NO: 2 containing 134 amino acids in the present application was disclosed in the priority documents. Therefore, this application gets priority as of filing date of U.K 991804.1; 7/30/1999 for claims 27, 29, 32, 34, 35, 38, 43-44 and 46 with respect to SEQ.ID.NO: 2.

Election/Restriction

3. Applicant's election of Group I claims 27, 29, 32, 34, 35, 38, 43-44 and 46 drawn to polypeptide, SEQ ID NO: 2, in Paper No. 7 (4/22/03) without traverse is acknowledged.

Claims 28, 30-31, 33, 36, 37, 39-42, 45 and 47-48 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, said election made in Paper # 7,

Information Disclosure Statement

4. The Information Disclosure Statement has not been filed in this application.

Specification - Informalities

5. Applicant should follow the direction or order or arrangement in framing the specification as provided in 37 CFR 1.77(b) since this is a utility application filed in USA. The specification should include all the sections in order. For example: Claims should begin with "I claim" or "We claim" or "What is claimed is".

It is noted that Abstract of the Disclosure is missing. If applicant desires to include the abstract from PCT/EP 00/07291, the Office would consider and a copy of the abstract will be inserted in to the specification. There are no line numbers in the specification pages.

The Brief Description of Drawing is not present in the Specification.

Claim Objections

6. Claim 38 is objected to as it depends from a canceled "claim 21"

Claim Rejections - 35 USC 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor or carrying

8. Claims 27, 29, 32, 34, 38, 43-44 and 46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the interim guidelines on written description published June 15, 1998 in the Federal Register at Volume 63, Number 114, pp 32639-32645 (also available at www.uspto.gov). This is a written description rejection.

The claims are drawn to an isolated polypeptide comprising SEQ.ID.NO: 2 and an immunogenic fragment comprising at least 15 amino acids or 20 amino acids. Claims are also drawn to fusion protein and immunogenic composition comprising said fragments, pharmaceutically acceptable carrier and adjuvant.

The specification broadly describes as part of the invention, an isolated protein of SEQ ID NO: 2, which is encoded by BASB125 gene from *M.catarrhalis*, ATCC strain 43617. The specification also teaches on page 47 that this full-length protein contains 134 amino acids. However, the specification does not teach fragments or immunogenic composition or fusion protein comprising said fragments (i.e., 15 amino acids or 20 amino acids.)

The actual biological function of the protein represented as SEQ ID NO: 2 is not set forth in this specification. Applicants broadly describe the invention as embracing any deletion by use of language in which a specified percent of amino acids can be changed in the protein. USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she] invented what is claimed." (See Vas-Cath at page 1116).

Thus, an isolated polypeptide consisting of SEQ ID NO: 2 meets the written description provision of 35 U.S.C. 112, first paragraph for the reasons set forth below.

The specification fails to teach an isolated polypeptide fragments of SEQ ID NO: 2 and it is noted that the claimed fragments do not exist as an invention independent of their function in encoding a protein, SEQ.ID.NO: 2. The actual structure or other relevant identifying characteristics of each protein fragment having the claimed properties of the protein can only be determined empirically by actually making every nucleic acid that encodes the recited fragments and testing each to determine whether such a fragment has the particularly disclosed properties of full length protein. For example, if there is a well-established correlation between structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its function. This specification does not teach such, and

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the art is devoid of this correlation for SEQ ID NO: 2 protein with undetermined function. There is no written description support for an isolated fragments comprising 15 amino acids or 20 amino acids or immunogenic composition or fusion protein comprising said fragments as claimed.

The isolated polypeptide comprising SEQ ID NO: 2 are uncharacterized by this specification and are not asserted to belong to any known family of proteins. The specification fails to teach the structure or relevant identifying characteristics of a representative number of SEQ.ID.NO: 2 fragments, sufficient to allow one skilled in the art to determine that the inventor had possession of the invention as claimed. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 U5PQ2d 1601, 1606 (CAFC 1993) and Amgen Inc V Chugai Pharmaceutical Co Ltd., 18 U5PQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 U5PQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

9. Claims 27, 29, 32, 34, 38, 43-44 and 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide consisting of the amino acid sequence SEQ ID NO: 2, fusion protein comprising the amino acid sequence SEQ ID NO: 2 does not reasonably provide enablement for an isolated polypeptide comprising a fragment of at least 15 or 20 amino acids or vaccine composition comprising said fragments of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches the production of recombinant BASB 125 encoding a polypeptide comprising 134 amino acids from *Moraxella catarrhalis* strain ATCC 43617. The

specification discloses the claimed polypeptide as an immunogen (pages 51-62) and formulating the compositions in Freund's adjuvant to immunize mice for preparing antibodies. However, the specification fails to teach an isolated polypeptide comprising a fragment of at least 15 or 20 amino acids or vaccine composition comprising said fragments of SEQ ID NO: 2. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid sequences (i.e. fragments) for different aspects of biological activity cannot be predicted a priori and must be determined empirically on a case-by-case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological-activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3): 1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol. 1991, 5(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis in proteins. Such proteins differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural

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components to both biological function and immunological recognition. Applicants have not taught which residues of SEQ ID NO: 2 can be varied and still achieve a polypeptide that is functional as a vaccine or is capable of use as a diagnostic using immunological means of recognition. The specification has not conceived any other functionally equivalent protein fragment and does not set forth the general tolerance to substitutions and where substitutions could be made. Since, the specification lacks a written description of any fragment of SEQ ID NO: 2, it is not enabled for this language because it fails to enable the skilled artisan to envision the detailed chemical structure of the claimed polypeptide fragment of SEQ ID NO: 2 respectively, as well as how to use the polypeptide fragment, one of skill in the art would be unable to produce these polypeptide. In view of the unpredictability of the art, the lack of teachings of the specification, it would require undue experimentation on the part of the skilled artisan to practice the invention as claimed.

10. Claims 27 and 43-44 (as a vaccine composition only) are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Instant claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed.Circ.1988) as follows:

(1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The definition of "vaccine" is broad, it is not so broad to cover any use of a substance on or in the body of a subject, only those uses intended to prevent, treat, or cure a disease within the animal to which the substance was administered.

Enablement of a "vaccine composition" is considered to rest on a teaching of *in vivo* administration for purposes consistent with the intended use disclosed in the specification. The disclosed intended use for the claimed vaccine is for the treatment of otitis media and respiratory disease caused by *Moraxella catarrhalis* infections. Thus, the nature of the invention is a therapeutic composition used in treatment or prevention. In the instant application, the animal to which the claimed composition is administered is merely being used as a bioreactor to make the antibodies (example 5) that will ultimately be used *in vitro*. In addition, the instant specification does not teach how to use the composition, without undue experimentation, for the prevention, treatment, or cure of a disease in the animal to which the substance is administered.

The specification teaches the production of recombinant BASB 081 encoding a polypeptide comprising 919 amino acids from *Moraxella catarrhalis* strain ATCC 43617. In the instant application, there is insufficient guidance which would enable one skilled in the art to use the claimed compositions for their intended purpose, viz., for the generation of a protective immune response against otitis media and respiratory disease caused by *Moraxella catarrhalis* infections. At the time the invention was made, vaccines comprising the claimed polypeptide were not routinely used for the treatment of otitis media and respiratory diseases. The specification lacks guidance by way of general methods or working examples which teach an "effective amount" of the vaccine which would be used for this purpose. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art, such as immunotherapy of otitis media and respiratory diseases. It is unpredictable whether the claimed composition, which is disclosed as being only immunogenic, would have the added

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property of generating the protective immune response sufficient to inhibit the otitis media and respiratory diseases because the prior art discloses that vaccine development is at the antigen identification stage and testing of these protective antigens is by testing them in animal models or clinical testing of these antigens (see review article by McMichael, 2000, *Microbes and Infection* 2; 561-568) The specification has not disclosed a link or nexus between the generation of protective antibodies and use in the above disorders. Further, it is not routine in the art of immunotherapy to use the claimed compositions for this purpose. Accordingly, there is no objective basis upon which the skilled artisan would reasonably be able to determine or predict an amount of the claimed composition/vaccine effective for its intended use. Therefore, undue experimentation would be required to make and use the invention.

Claim Rejections - 35 USC 112, second paragraph

11 The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

12. Claims 27, 29, 32, 34, 35, 38, 43-44 and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 is rejected as being vague and not clear in reciting " T-cell immune response to a polypeptide having the sequence of SEQ.ID.NO: 2." It is not clear what T-cell immune response applicant intend to mean. Does applicant intend to mean T-cell mediated immune response, which induces TH1 type immune response or something else? It is not clear whether T-cell mediated response is to the polypeptide SEQ.ID.NO: 2 or something less than a polypeptide SEQ.ID.NO: 2 since the claim recites "a polypeptide".

Claim 44 is rejected for the recitation of " one other M.catarrhalis antigen". It is difficult to understand the metes and bounds of one other M.catarrhalis antigen as written.

Claim Rejections - 35 USC 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 27, 29, 43-44 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Helminen et al 1994 (J.Infec.Dis, 170; 867-872).

Claims are directed to an isolated polypeptide comprising (a) an amino acid sequence matching SEQ.ID.NO: 2 and said composition when administered with a carrier induces an antibody response or t-cell response.

Helminen et al 1994 disclose an isolated polypeptide, outer membrane protein i.e., OMP from whole cell lysate in a buffer from M.catarrhalis. The antigen to which an immune response has to be elicited is in general in a hydrophilic phase (i.e., buffer). Monoclonal antibodies were produced by administering (i.e., immunizing) whole cell lysate antigens to mice (page 867, right column through page 868, left column, first paragraph). Applicant's use of the open-ended term "comprising " in the claim 27 fails to exclude unrecited steps or ingredients and leaves the claims open for inclusion of unspecified ingredients, even in major amounts. Therefore, the claims read on the disclosed isolated polypeptide, OMP from M.catarrhalis. Whole cell lysate from M.catarrhalis appears to contain an isolated polypeptide that matches SEQ.ID.NO: 2. Characteristics such as SEQ.ID.NO: 2 are considered as inherent properties of the polypeptide

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that was present in the lysate disclosed by the prior art. See In re Horvitz, 168 F 2d 522, 78 U.S.P.Q. 79 (C.C.P.A. 1948) and Ex parte Davis et al., 80 U.S.P.Q. 448 (PTO d. App. 1948). Since the Office does not have the facilities for examining and comparing applicants' claimed isolated polypeptide comprising SEQ.ID.NO: 2 with the polypeptide of prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

It is acknowledged that weight is given to every term in claims. This is why the instant claims drawn to vaccine are scrutinized differently from a composition claim under 112, first paragraph. However, under prior art rejections, the term vaccine must be weighed with the structural limitations of the claim. If the vaccine merely comprises a known composition, the term carries little weight absent evidence of structural difference. Of course, the existence of an unobvious structural difference would define over the prior art.

Status of Claims

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padma Baskar whose telephone number is (703) 308-8886. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4 PM EST

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Padma Baskar Ph.D.

LYN
LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600